



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/571,991

03/15/2006

Laurent Francois Andre Hennequin

09963.0008

5523

22852

7590

08/19/2008

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER
LLP

901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER

WILLIS, DOUGLAS M

ART UNIT

PAPER NUMBER

4161

MAIL DATE

DELIVERY MODE

08/19/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/571,991	Applicant(s) HENNEQUIN ET AL.	
	Examiner DOUGLAS M. WILLIS	Art Unit 4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 July 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 38-71 is/are pending in the application.
- 4a) Of the above claim(s) 44-71 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 38-43 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>03-15-06; 07-11-06; 01-09-07; 07-14-08</u> . | 6) <input type="checkbox"/> Other: _____ |

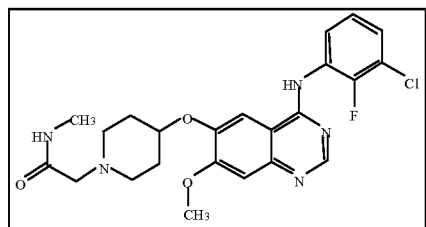
DETAILED ACTION

Status of the Claims / Priority

Claims 38-71 are pending in the current application. According to the *Amendments to the Claims*, filed July 14, 2008, claims 1-37 were cancelled and claims 38-71 were added. This application is a 35 U.S.C. § 371 National Stage Filing of International Application No. PCT/GB2004/03937, filed September 15, 2004, which claims priority under 35 U.S.C. § 119(a-d) to: a) EP 03292309.6.7, filed September 19, 2003 and b) EP 04291248.5, filed May 14, 2004.

Restrictions / Election of Species

Applicant's provisional election of the following, with traverse, in the reply filed on July 14, 2008, is acknowledged: a) Group I, claims 38-43; and b) compound - example I, p. 58,



shown left, and hereafter referred to as 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)-piperidin-4-yl]oxy}quinazoline. Affirmation of this election

must be made by applicant in replying to this Office action.

The traversal is on the ground(s) that: a) following entry of the *Amendments to the Claims*, filed July 14, 2008, search of the claimed subject matter falling within Group I will substantially, if not completely, overlap with the search for the claimed subject matter regarding methods outlined in Groups II and III, respectively; and b) any burden originally perceived by the Office has been significantly reduced in that the new compound and method claims have been reduced to a single species. This is not found persuasive because: a) it is not necessary for a reference to be anticipatory to indicate the lack of a *special technical feature*; b) the standard

Art Unit: 1625

for lack of unity in 371 practice is dissimilar to that of 35 U.S.C. § 102; c) although a technical feature is present and links the aforementioned claims, the prior art illustrates that this technical feature is not *special*; and d) the multiple inventions in the instant application are independent or distinct for the reason(s) disclosed in the *Requirement for Restriction / Election of Species*, as stated above. Furthermore, there would be a serious burden on the examiner if restriction was not required because the inventions have acquired a separate status in the art due to their divergent subject matter and would require a different field of search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 44-71 were withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Thus, a first Office action on the merits of claims 38-43 is contained within.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

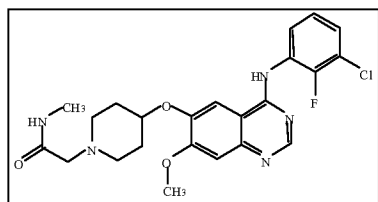
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 38-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bradbury, et al. in WO 03/082831 and Patani, et al. in *Chem. Rev.*, 96, **1996**, pp. 3147-3176.

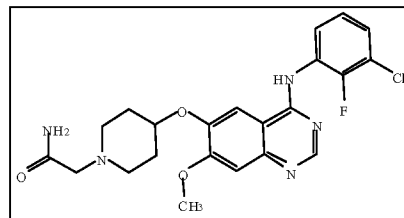
The instant application recites a compound chosen from 4-(3-chloro-2-fluoroanilino)-7-



methoxy-6- {[1-(N-methyl-carbamoylmethyl)piperidin-4-yl]oxy}-quinazoline, pharmaceutically acceptable salts and pharmaceutical compositions thereof, shown to the right above, which possesses

anti-tumor activity.

Bradbury, et al. (WO 03/082831) teaches 2-(4-(4-(3-chloro-2-fluorophenylamino)-7-methoxyquinazolin-6-yloxy)piperidin-1-yl)acetamide, pharmaceutically acceptable salts and pharmaceutical compositions thereof, shown to the right, as an antiproliferative agent [example 11, p. 106; pharmaceutically acceptable salts - p. 81, lines 27-32; and pharmaceutical compositions - p.91, line 28].



Patani, et al. (*Chem. Rev.*, 96, **1996**) teaches the relationship between -CH₃ groups and -H atoms as monovalent bioisosteres, which exert similar biological activity [p. 3148; column 1], via a direct adaptation of Grimm's Hydride Displacement Law [p. 3152, section A4; p. 3153 - column 1, ¶ 2; p. 3163, Table 12 - column 2].

The only difference between the instantly recited 4-(3-chloro-2-fluoroanilino)-7-methoxy-6- {[1-(N-methyl-carbamoylmethyl)piperidin-4-yl]oxy}quinazoline and Bradbury's 2-(4-(4-(3-chloro-2-fluorophenylamino)-7-methoxyquinazolin-6-yloxy)piperidin-1-yl)acetamide is the instantly recited substituted quinazoline has a methylacetamido substituent on the 1-position (nitrogen) of the piperidine ring, whereas Bradbury's quinazoline has an acetamido substituent

Art Unit: 1625

on the 1-position (nitrogen) of the piperidine ring.

The MPEP § 2144.09 states “Compounds which are position isomers, having the same radicals in physically different positions on the same nucleus, are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. {*In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977)}.

Similarly, the courts have recognized that *there is little difference between the ortho- and para- positions occupied by -F in the anilino-substituted quinazolines and pharmaceutical compositions above, as similar circumstances have arisen many times. As a matter of fact, it is well established that position isomers are structurally prima facie obvious, even in the absence of a teaching to modify. The isomers are expected to have the same method of preparation and generally the same properties. It is this expectation that is deemed the motivation for preparing such isomers.* (See: *Ex parte Englehardt*, 208 USPQ 343, 349; *In re Mehta*, 146 USPQ 284, 287; *In re Surrey*, 138 USPQ 67; *Ex Parte Ullyot*, 103 USPQ 185; *In re Norris*, 84 USPQ 459; *Ex. Parte Naito*, 168 USPQ 437, 439; *Ex parte Allais*, 152 USPQ 66; *In re Wilder*, 166 USPQ 545, 548; *Ex parte Henkel*, 130 USPQ 474; *Ex parte Biel*, 124 USPQ 109; *In re Petrzilka*, 165 USPQ 327; *In re Crownse*, 150 USPQ 554; *In re Fouche*, 169 USPQ 431; *Ex parte Ruddy*, 121 USPQ 427; *In re Wiechert*, 152 USPQ 249, *In re Shetty*, 195 USPQ 753; *In re Jones*, 74 USPQ 152, 154).

Furthermore, *position isomerism has been used as a tool to obtain new and useful drugs (Ex parte Englehardt) and... is fact of close structural similarity (In re Mehta).* Similarly, *a novel useful chemical compound, which is homologous or isomeric with compounds of the prior art, is unpatentable unless it possesses some unobvious or unexpected beneficial property not*

Art Unit: 1625

possessed by the prior art compounds. (In re Schechter and LaForge, 98 USPQ 144, 150). Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds... and a known compound may suggest it's analog or isomers, either geometric (cis v. trans) or positional isomers (e.g. ortho v. para). (In re Deuel 34 USPQ2d 1210, 1214).

Thus, since: a) Bradbury teaches 2-(4-(4-(3-chloro-2-fluorophenylamino)-7-methoxyquinazolin-6-yloxy)piperidin-1-yl)acetamide, which has a fluorine in the 2-position of the aniline moiety; b) Patani teaches -CH₃ groups and -H atoms as monovalent bioisosteres, which exert similar biological activity; c) the MPEP § 2144.09 states that positional isomers are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties; and d) the courts have recognized that positional isomers are structurally *prima facie* obvious and are expected to have the same method of preparation, one having ordinary skill in the art, at the time this invention was made, would have been motivated to combine the teachings of both Bradbury and Patani and: a) methylate the acetamido substituent on the 1-position (nitrogen) of the piperidine ring in Bradbury's anilino-substituted quinazoline, pharmaceutically acceptable salt or pharmaceutical composition thereof, to form a methylacetamido anilino-substituted quinazoline, pharmaceutically acceptable salt or pharmaceutical composition thereof, with a reasonable expectation of success and similar therapeutic activity, rendering claims 38-43 obvious.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any

Art Unit: 1625

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DOUGLAS M. WILLIS, whose telephone number is 571-270-5757. The examiner can normally be reached on Monday thru Thursday from 8:00-6:00 EST. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan, can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D. M. W./

Examiner, Art Unit 4161

Application/Control Number: 10/571,991
Art Unit: 1625

Page 8

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4161